REMARKS

This amendment is being filed in response to Office Action mailed July 2, 2003. Claims 1 to 39 and 41 to 72 are pending. Claims 1 to 39 and 41 to 64 stand withdrawn from consideration as directed to a non-elected invention. By the present amendment, claims 66 to 70 have been canceled without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. Accordingly, upon entry of the amendment, claims 65, 71 and 72 are under consideration.

Regarding the Amendments

The amendments to claims 65, 71 and 72 are supported by the specification or were made to address various informalities, and place the claims in better condition for allowance or appeal. In particular, the amendment to claim 65 to recite that "the agonist anti-MAFA antibody or the antigen binding subsequence of the agonist anti-MAFA antibody binds to a MAFA polypeptide set forth in any of SEQ ID NOs: 1, 3 or 5," is supported, for example, at page 12, line 27, to page 13, line 2. The amendment to claim 65 to recite that the subsequence of an agonist anti-MAFA antibody is "an antigen binding" subsequence was made to rephrase the claim in response to the Examiner's suggestion. The amendment is also supported, for example, at page 11, lines 13-20. The amendment to claim 65 to recite "in vitro or *ex vivo*" is supported as set forth for claim 66. The amendment to claim 71, which depends from claim 65, to also recite "an antigen binding," was made to provide claim language consistency and, therefore, addresses an informality. The amendments to claims 71 and 72 to alter claim dependency were made due to typographical errors in the claim numbering and, therefore, addresses an informality.

Thus, as the amendments to the claims are supported by the specification or were made to address various informalities, no new matter has been added. Furthermore, as the amendments place the claims in better condition for allowance or appeal entry thereof is respectfully requested.

I. OBJECTION TO THE DISCLOSURE

The disclosure stands objected to due to an informality. As to the ATCC No., Applicants respectfully request that this objection be held in abeyance until notification of allowable subject matter.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 65 to 72 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. The grounds for rejection appear to be based upon the alleged absence of guidance for "any agonist anti-MAFA antibody," for "any subsequence of any anti-MAFA antibody," for "preventing or stimulating NK or T cell cytolytic activity....in vivo."

The specification enables claims 65 to 72 prior to the present amendment. Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, claims 66 to 70 have been canceled herein without prejudice, and claims 65, 71 and 72 have been amended as set forth above. The rejection will therefore be addressed as it may pertain to the amended claims.

Applicants respectfully remind the Patent Office that the proper test for enablement under 35 U.S.C. §112, first paragraph, is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Applicants also respectfully remind the Patent Office that the Federal Circuit has repeatedly held that "the fact that experimentation is complex does not necessarily make it undue, if the art typically engages in such experimentation." See, for example, *In re Wands*, 858 F.2d 731, 735-37 (Fed. Cir. 1988).

Here, amended claims 65, 71 and 72 recite that "the agonist anti-MAFA antibody or the antigen binding subsequence of the agonist anti-MAFA antibody binds to a MAFA polypeptide set forth in any of SEQ ID NOs: 1, 3 or 5." Given the guidance in the specification and knowledge in the art one skilled in the art could practice claims 65, 71 and 72 without undue experimentation.

First, the level of skill in the art for producing polyclonal and monoclonal antibodies is high. In this regard, the specification discloses how to produce polyclonal and monoclonal antibodies including anti-MAFA antibodies using routine methods known in the art at the time of

the invention, as evidenced by the references cited therein (see, for example, page 22, line 16 to page 23, line 12; page 26, line 24, to page 28, line 11; and page 28, line 21, to page 29, line 11). As to producing modified antibodies (e.g., having substitutions, deletions and additions), given the knowledge of antibody structure and function in the art at the time of the invention, one skilled in the art would know the regions that may be modified without destroying antigen binding activity. For example, one skilled in the art would know that the six complementarity determining regions (CDR) of an antibody, which are approximately 70 amino acids long, form the antigen binding site (Chothia and Lesk, J Mol Biol. 196:901 (1987)). The skilled artisan would also know that the constant region is not required for antigen binding. Thus, in view of this knowledge the skilled artisan would know that non-conservative substitutions and large deletions in the CDRs are likely to have a deleterious affect on binding activity, whereas mutating or deleting one or more amino acids in the constant region will have minimal if any affect on binding activity. Furthermore, the specification discloses methods for producing antibodies having amino acid substitutions, deletions and additions, mimetics, and humanized forms, and such methods were also routine in the art at the time of the invention as evidenced by the references cited therein (see, for example, page 11, line 13, to page 12, line 15; page 13, line 11, to page 15, line 11; and page 21, lines 8-21). Thus, in view of the specification and of knowledge in the art the skilled artisan could produce agonist anti-MAFA antibodies including modified forms without undue experimentation.

Second, the specification discloses assays for identifying anti-MAFA antibodies having agonist activity. For example, the specification discloses assays for measuring cytotoxic activity of NK and CTL cells, and such methods were also routine in the art at the time of the invention, as evidenced by the references cited therein (see, for example, page 28, lines 12-19 and the Sentman and Franco references cited therein; and page 29, line 20, to page 30, line 7). Thus, in view of the specification and of knowledge in the art one skilled in the art could identify anti-MAFA antibodies having agonist activity without undue experimentation.

Third, the specification exemplifies producing two anti-MAFA antibodies, 1F10 and 7B5 (page 28, line 21 to page 29, line 19), having agonist activity (page 29, line 20, to page 30, line 7; see, also, page 31, lines 4-18). The fact that 1F10 and 7B5 agonist anti-MAFA antibodies can be produced without undue experimentation corroborates that agonist anti-MAFA antibodies as a class can be produced without undue experimentation.

Thus, given the guidance in the specification and knowledge in the art for producing polyclonal and monoclonal antibodies including fragments, mimetics, modified forms, variants (e.g., amino acid substitutions, additions and deletions) and humanized forms, and further in view the fact that the specification exemplifies two agonist anti-MAFA antibodies indicating that such antibodies as a class can be produced using methods known in the art at the time of the invention, undue experimentation would not be required to produce agonist anti-MAFA antibodies and antigen binding subsequences of agonist anti-MAFA antibodies. Consequently, as undue experimentation would not be required to obtain such antibodies, claims 65, 71 and 72 are adequately enabled.

Fourth, as previously pointed out the cited Kuby *et al.*, Ngo *et al.* and Abaza *et al.* references were published in 1992 and in 1994 and cannot fairly be said to represent the start of the art at the time the application was filed in 2001. Furthermore, Kuby *et al.*, Ngo *et al.* and Abaza *et al.* describe the effect of *antigen* alterations on immunogenicity. However, one skilled in the art could produce additional anti-MAFA antibodies and modified forms having MAFA binding affinity and agonist activity without altering MAFA antigen. Thus, the skilled artisan would not need to know how altering MAFA affects immunogenicity. Consequently, as additional agonist anti-MAFA antibodies can be produced without altering MAFA antigen, Kuby *et al.*, Ngo *et al.* and Abaza *et al.* are irrelevant to producing agonist anti-MAFA antibodies, and are therefore also irrelevant to enablement of claims 65 to 72. Further in this regard, the Federal Circuit's position on this issue is clear: the failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987).

To reiterate, the present case is analogous to *In re Wands*. In *Wands*, the Federal Circuit recognized that "there was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 737. The court therefore concluded that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. In the present case as in *Wands*, the level of skill in the art is high and the methods for producing anti-MAFA antibodies are disclosed by the specification or were known in the art at the time of the invention. Thus, as in *Wands*, undue experimentation would not be required to obtain additional agonist anti-MAFA antibodies as

claimed. Accordingly, claims 65, 71 and 72 are adequately enabled and the rejection under 35 U.S.C. §112, first paragraph, is improper and must be withdrawn.

Applicants also wish to point out that although claims 66 to 70, directed to *in vivo* uses, have been canceled, these claims are also adequately enabled. First, Applicants again remind the Patent Office that the proper standard for enablement is whether one skilled in the art would accept that the model is reasonably correlating to the condition. *In re Branna*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). A rigorous or an invariable exact correlation is *not* required. *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *Emphasis added.*

Here, claims 66 to 70 recite inhibiting an NK- or a T cell expressed cell surface MAFA binding to a ligand on a target cell by providing an agonist anti-MAFA antibody or subsequence of an agonist anti-MAFA antibody that inhibits the binding of the NK- or the T cell-expressed cell surface MAFA to its target cell ligand; and contacting the agonist anti-MAFA antibody or subsequence of the agonist anti-MAFA antibody to the NK or the T cell or the target cell in an amount sufficient to inhibit cell surface MAFA binding to the ligand on the target cell. As pointed out in Applicants' previous Response, the cytotoxic activity assays disclosed in the specification are predictive of what one skilled in the art would expect *in vivo* because (1) MAFA, also referred to as KLRG1, is a naturally occurring molecule expressed on NK cells and virally activated T cells that inhibits cytokine production and NK cell-mediated cytotoxicity (see, for example, the specification page 2, lines 3-5, page 9, lines 5-9; and page 10, lines 13-15 and lines 20-30; see also, Corral *et al.*, *Eur. J. Immunol.* 30:920 (2000); McMahon *et al.*, *J. Immunol.* 169:1444 (2002); and Beyersdorf *et al.*, *Eur. J. Immunol.* 31:3443 (2001)); and (2) it is known that NK and T-cells participate in immune responsiveness including killing virally infected cells and tumor cells. (Herberman, RB, *Semin. Oncol.* 29:27 (2002); Miller, JS, *Cancer Invest.* 20:405 (2002); and Brutkiewicz *et al.*, *Crit. Rev. Oncol. Hematol.* 41:287 (2002)). Thus, given the fact that MAFA is an endogenous molecule expressed on NK cells and T-cells which modulates cytotoxicity and cytokine secretion; and that NK cells and T-cells mediate immune response and participate in killing virally infected cells and anti-tumor responses *in vivo*, the in vitro data disclosed in the specification demonstrating that agonist anti-MAFA antibody decreases NK cytotoxicity is evidence sufficient to predict *in vivo* activity. Given that the skilled artisan would predict *in vivo* activity of agonist anti-MAFA antibody based upon the in vitro data disclosed in the specification, the in vitro model "reasonably correlates" with the *in vivo* condition.

Significantly, as the initial burden is on the Examiner to give reasons for a lack of enablement, the Examiner *must also give reasons* for a conclusion of a lack of correlation for an *in vitro* or *in vivo animal model example*. See, for example, M.P.E.P. §2164.02; *Emphasis added.* Here, however, the Examiner has failed to address the correlation between the in vitro data disclosed in the specification discussed above and in the record, let alone provide a reason for any lack of correlation. Thus, in view of the failure to provide reasons for a lack of correlation which the Examiner must, the grounds for rejection under 35 U.S.C. §112, first paragraph, due to an alleged lack of enablement for *in vivo* uses, is clearly improper.

The rejection of claims 65 to 72 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description is respectfully traversed. The grounds for rejection appear to be based upon the alleged lack of written description for "any agonist anti-MAFA antibody," and for "any subsequence of any anti-MAFA antibody."

An adequate written description for claims 65 to 72, prior to the present amendment, is provided. Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, claims 66 to 70 have been canceled without prejudice, and claims 65, 71 and 72 have been amended as set forth above. The rejection will therefore be addressed as it may pertain to the amended claims.

To satisfy the written description requirement under 35 U.S.C. §112, first paragraph, an applicant "must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Under the Guidelines for Determining Compliance with the Written Description Requirement, possession may be shown in a variety of ways including "describing distinguishing identifying characteristics." M.P.E.P. §2163.02.

Here, amended claims 65, 71 and 72 recite that "the agonist anti-MAFA antibody or the antigen binding subsequence of the agonist anti-MAFA antibody binds to a MAFA polypeptide set forth in any of SEQ ID NOs: 1, 3 or 5." As set forth above, the specification teaches how to make such antibodies, and exemplifies producing two antibodies having agonist activity, 1F10 and 7B5. Thus, the skilled artisan would know of at least two specific agonist anti-MAFA antibodies.

As to additional agonist anti-MAFA antibodies, such antibodies would be known to the skilled artisan based upon the guidance in the specification and knowledge in the art. One particular non-limiting example of an agonist anti-MAFA antibody would be a humanized form of 1F10 and 7B5. Another non-limiting example of an agonist anti-MAFA antibody would be a 1F10 and 7B5 with a conservative amino acid substitution in a constant region. Additional examples of agonist anti-MAFA antibodies would be known to one skilled in the art, based upon their knowledge of antibody structure and function as well as their knowledge of methods of producing modified antibodies, as discussed above and in the record. For example, as the skilled artisan understands that CDR's mediate antigen binding, the skilled artisan would know agonist anti-MAFA antibodies having one or more substitutions outside of a CDR.

As to antigen binding subsequences of anti-MAFA antibody, the specification discloses Fab, VL, VH, CL and CH1 domains; Fv; dAb and isolated CDR, to name a few (page 11, line 19, to page 12, line 15). Given the fact that these and other antigen binding subsequences of antibodies are known to those skilled in the art, the skilled artisan would merely apply that knowledge to know antigen binding subsequences of anti-MAFA antibody. For example, the skilled artisan would know the Fab, VL, VH, CL and CH1 domains; Fv; dAb and isolated CDR antigen binding subsequences of the 1F10 and 7B5 anti-MAFA antibodies, in view of the guidance in the specification and knowledge in the art, as discussed above and in the record.

Finally, as to the citation of *Regents of the University of California v. Eli Lilly & Co.*, this case was decided against the patentee because only a single rat insulin sequence was disclosed in the patent specification. The court held that disclosure of a single sequence did not provide an adequate written description for claims directed to "vertebrate" or "mammalian" insulin genus. *Eli Lilly* 119 F.3d 1559 (Fed. Cir. 1997). Here, in stark contrast to *Eli Lilly* the specification teaches agonist anti-MAFA antibodies and antigen binding subsequences. Furthermore, unlike *Eli Lilly* one skilled in the art would recognize agonist anti-MAFA antibodies and antigen binding subsequences in view of the guidance in the specification and of knowledge in the art. Accordingly, the claims prior to and following entry of the present amendment are clearly distinguishable from the claims of the patent at issue in *Eli Lilly*.

In sum, in view of the fact that one skilled in the art would be apprised of agonist anti-MAFA antibodies and antigen binding subsequences of agonist anti-MAFA antibodies, an adequate written description for agonist anti-MAFA antibodies and antigen binding

subsequences of agonist anti-MAFA antibodies is provided. As such, claims 65 to 72 are adequately described, and Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description, be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 65 to 71 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is respectfully traversed. The grounds for rejection are based upon a the term "subsequence" in claims 65, 68 and 71, and incorrect numbering of the claims from which claims 68 to 71 depend.

As set forth above, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, claims 66 to 70 have been canceled without prejudice, and claims 65 and 71 have been amended as suggested by the Examiner to recite "an antigen binding" subsequence. Claims 71 and 72 have been amended to provide the correct the numbering of the claims from they depend.

In view of the amendments and foregoing remarks, claims 65, 71 and 72 are clear and definite. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 65, 71 and 72 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

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